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09/061,417	04/16/1998	ERIC N. OLSON	UTSD:548	1649

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/061,417	OLSON ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-8 and 10-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 4, 9 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9, pertaining to lack of a clear description of a small molecule inhibitor of NF-AT3 remains for reasons already of record in paper No.15.

Applicant asserts that unlike the *Lilly* case, where a single species was held inadequate to support a genus, the present specification provides at least three different types of molecules, single chain antibodies, GATA4 mimetics, and small molecules. Applicant further assertst that thus the genus is far better supported here than in *Lilly,* and that, at the time the invention was filed, Martinez-Martinez reported DTC's which are small molecule inhibitors of NF-ATF-3. Applicant asserts that the common characteristic is inhibition of NF-AT-3 activity. In addition, Applicant asserts that the Examiner rejection of GATA4-based inhibitors, which is based on the grounds that the

binding site on GATA4 for NF-AT3 is not disclosed in the specification is incorrect. Applicant asserts that Example 3 clearly defines a region of GATA4 that is sufficient to interact with NF-AT3, and thus this description is far more important that the Examiner has admitted.

Applicant concludes that since NF-AT3 is a key player in hypertrophic signaling, it is therefore, sufficient to describe methods of treatment for cardiac hypertrophy that focus more on the desired activity of the agents, and less on their structure.

The recitation of Martinez-Martinez is acknowledged.

Applicant's arguments set forth in paper No.17 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the Examiner rejection is based on the ground that the **configuration** of the second zinc finger of GATA4, a site for binding of GATA4 to NF-AT3, is not known, and not on the ground that the binding site on GATA4 for NF-AT3 is not disclosed in the specification, as asserted by Applicant.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In other words, a precise definition, such as by structure, formula, chemical name, or physical properties, for the claimed small molecules that bind to and inactivate NF-AT-3 is missing in the specification.

Further, the claims encompass three different categories of small molecules: single chain antibodies, GATA4 mimetics, and small molecules such as DTCs, and cyclosporin A. Applicant recites in the response only a single category, the antioxidant dithiocarbamates DTC's, which are small molecules that are inhibitors of NF-AT3. However, it is noted that DTC's are not disclosed in the specification for use in the claimed method, and that it is not clear whether DCT's actually bind to NF-AT3, which is the limitation of claims 4 and 9.

In addition, concerning the category of small molecule single chain antibodies, the structure of the claimed single chain antibody that inactivates NF-AT3 by blocking the active site of NF-AT3, is not known, because the active site of NF-AT3, where the claimed antibody presumably binds, is not disclosed.

Moreover, the structure of the other category of small molecules, GATA4 mimetics, however, are not disclosed in the specification. The specification discloses that the claimed mimetics may be "sterically" similar to the actual target compound (p.29). There is however no information regarding the relation of structure to function. As stated in previous Office action, although molecular modeling is known in the art, the structure of the claimed small molecule inhibitors is unpredictable, especially in view of the fact that the configuration of the second zinc finger of GATA4, a site for binding of GATA4 to NF-AT3, is not known.

Further, concerning Applicant's assertion that it is sufficient to describe methods of treatment for cardiac hypertrophy that focus more on the desired activity of the agents, and less on their structure, this argument is not found to be persuasive. The

court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description. In other words, when applied to the claimed method using the claimed small molecules which are GATA4 mimetics, definition of the claimed mimetic small molecule inhibitors, via the function of said mimetics alone, would not meet the requirement for a written description.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9, pertaining to lack of enablement for a method of treating hypertrophy comprising contacting a cardiomyocyte with a small molecule inhibitor of NF-AT3 remains for reasons already of record in paper No.15.

Applicant argues as follows:

1) Applicant asserts that it is well established that examples are not required to prove enablement.

2) Applicant recites the references by Ichida, 2001, and Xia, 2000, stating that there is considerable evidence that NF-AT3 (a.k.a. NFATc4) is expressed in cardiac myocytes.

3) Applicant recites the reference by Suzuki et al, 1999, stating that while there is no definitive proof of *in vivo* binding between GATA4 and NF-AT3, the teaching by Suzuki et al that GATA4 DNA binding and NF-AT activity show similar kinetics when cells are induced by AngII lends further credibility of the data provided in Example 3.

4) Applicant asserts that the specification identifies in example 3 the Rel homology domain of NF-AT3 as possible site for facilitating NF-AT3 binding to GATA4. Applicant asserts that Applicant needs not know anything about the site to enable their method, only that a small molecule inhibitor, e.g. a DTC, actually functions as an inhibitor.

5) Applicant asserts that the Examiner is unnecessarily focusing the antibody disclosure to argue that the appropriate targeting cannot be achieved. For example, the use of GATA4 mimetics and DTC's do not suffer from the perceived shortcomings of antibodies. In addition, Applicant asserts that it is well known that nuclear targeting signals can facilitate transport of proteins back into the nucleus, and thus there are means to address such problems. Furthermore, Applicant asserts that the generalized discussion of stability, half-life, proteolytic degradation, tissue penetration, circulation to target areas, etc... such arguments can be made against almost any therapeutic approach, and that, however, there are ways to address each of these issues, such as encapsidation, localized administration, or modification. This litany of potential problems is an insufficient grounds for finding lack of enablement.

Applicant's arguments set forth in paper No.17 have been considered but are not deemed to be persuasive for the following reasons:

The recitation of the references by Ichida, 2001, Xia, 2000, Suzuki et al, 1999 is acknowledged. It is noted that the arguments in items 2 and 3, and the references could not be considered because the references were not submitted with the amendment.

Concerning Applicant assertion that it is well established that examples are not required to prove enablement, MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Since little is known in the art about treating hypertrophy, using a small molecule inhibitor that bind to and inactivates NF-AT3, and since it is questionable that NF-ATF-3 is continuously activated in the hearts of patients having cardiac hypertrophy, and is responsible for up-regulation of cardiac hypertrophic genes *in vivo* via binding with GATA4 *in vivo*, and further since there is overwhelming evidence that treatment of hypertrophy using a small molecule that binds to and inactivates NF-AT3 is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling.

One cannot predict that NF-AT3 actually interacts with GATA4 in nature, in cardiomyocyte cells *in vivo*, because of the following reasons: The interaction between

NF-AT3 and GATA4 in example 2 is only from mouse embryo libraries, which are not cardiomyocyte cells, and one cannot predict that there is the same interaction between NF-AT3 and GATA4 in cardiomyocyte cells . Further, although BNP promoter is up-regulated in the presence of GATA4, NF-AT3 and calcineurin in cardiomyocyte cells, as disclosed in example 4, the cardiomyocyte cells are however transfected with GATA4, NF-AT3, the artifial condition of overexpression and overabundance of which could effect the distribution and thus forced interaction between GATA4 and NF-AT3. Further, the transfected calcineurin is in a mutant form, which is constitutively, i.e. continously, active. Thus the conditions of the transfected cells would not be even remotely similar conditions as in hypertrophic cardiomyocyte cells *in vivo.* Further, one could not apply *in vitro* conditions to *in vivo* conditions because of the following reasons: 1) cell culture artifacts are well known in the art, and 2) characteristics of cultured cell lines generally differ significantly from the characteristics of a primary cell, wherein specific cell-cell interactions and homeostatic regulation is lost in tissue culture, as taught by Freshney (of record). Thum T et al, 2001, of record, teach that the levels of expression of target genes of GATA-4 in cells in cultures are different as compared to those from freshly isolated cells.

Similarly, the transgenic mice having cardiac hypertrophy, wherein a transfected mutant NF-AT3, which is continously activated, and expressed in the hearts, do not represent a model for cardiac hypertrophy for human. Applicant has not shown that NF-AT3 is continously activated in the hearts of patients having cardiac hypertrophy, and is

responsible for up-regulation of cardiac hypertrophic genes via interaction with GATA4 *in vivo* in patients with cardiac hypertrophy.

The scope of the claims however encompasses a method for treating cardiac hypertrophy, which does not read on treating transfected cells or transgenic mice carrrying mutant NF-AT3, which is continously activated, and expressed in the hearts. It is clear that the disclosure in the specification is not commensurate in scope with the claimed invention.

Concerning Applicant's assertion that Applicant needs not know anything about the site of binding of the claimed small molecules to enable their method, only that a small molecule inhibitor, e.g. a DTC, actually functions as an inhibitor, this argument is not persuasive for the following reasons: The claims encompass a method of treating hypertrophy, using a small molecules which could be single chain antibodies, which bind to and inhibit the activities of NF-AT3. Although the specification discloses that the Rel homology domain of NF-AT3 is sufficient for the binding of NF-AT3 to GATA4, it is unpredictable that said region is necessary for the binding of NF-AT3 to GATA4. In other words, the epitope of the claimed antagonist single chain antibodies against NF-AT3 is not known. As discussed in the previous Office action, there is no teaching of the linear or three dimensional structures of the epitope for the claimed antibodies, as defined by Herbert et al (of record), wherein defining the epitope is not as easy as it seems, as taught by Greenspan et al (of record). Therefore, one of skill in the art would not know how to make and use the claimed method, using the small molecule single chain antibodies.

Concerning Applicant's assertion that the Examiner is unnecessarily focusing the antibody disclosure to argue that the appropriate targeting cannot be achieved, it is noted that 1) the NF-AT3 inhibitors, DTC's, are not disclosed in the specification, and 2) it is not clear whether DCT's actually bind to NF-AT3, which is the limitation of claims 4 and 9.

Concerning Applicant's assertion that there are ways to address each of the issues raised by the Office, e.g. stability, half-life, proteolytic degradation, tissue penetration, circulation to target areas, etc , by using nuclear targeting signals, encapsidation, localized administration, or modification, it is noted that the specification does not provide any teaching concerning how to overcome these issues, and that it is unpredictable that these issues could be overcome by the proposed means. Concerning the arguments that that nuclear targeting signals can facilitate transport of proteins such as the claimed single chain antibody small molecule back into the nucleus, it is unpredictable that said single chain antibody with encapsidation and/or modification by conjugated to nuclear targeting signals, or localized administered would enter not only the cell membrane but the nucleus of the cardiomyocytes in an effective amount for inhibiting NF-AT3. Further it is unpredictable that said small molecule single chain antibody conjugated to nuclear membrane signals is still in the configuration for interacting with and inhibits NF-AT3. The specification does not teach how to conjugate the claimed single chain antibody with the nuclear membrane signals such that the configuration of the single chain antibody is preserved, and that the nuclear membrane signals would not interfere with the binding of the single chain antibody and NF-AT3.

Further, in the absence of any disclosed relationship between treating hypertrophy and administration of a single chain antibody that inhibits NF-AT3, any information obtained from testing the claimed single antibody that is conjugated to a nuclear signal targeting, or encapsulated or localized administered would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696.

Concerning the use of DTC's for the claimed method of treating hypertrophy, DTC's has been shown by Martinez-Martinez et al as an inhibitor of NFAT only *in vitro* and in T cells. It is well known in the art that one could not apply *in vitro* conditions to *in vivo* conditions, due to cell culture artifacts, and significant differences in characteristics of cultured cell lines and a primary cell, wherein specific cell-cell interactions and homeostatic regulation is lost in tissue culture, as taught by Freshney and Thum et al (of record). Further, although DTC's is an inhibitor of NFAT in T cells, it is unpredictable that DTC's is active in cardiomyocytes, because different cells are have different properties and characteristics in responding to drugs.

Concerning the use of GATA4 mimetics for treating hypertrophy, the structure of the mimetics is not disclosed by the specification and is not predictable, *supra*, and one would not know how to use the claimed mimetics for treating hypertrophy.

Thus, there is overwhelming evidence that treatment of hypertrophy using a small molecule that binds to and inactivates NF-AT3 is unpredictable

In conclusion, although an example is not always required, but in view of the above, it would have been a burden for one of skill in the art to practice the claimed invention.

REJECTON UNDER 35 USC 102, NEW REJECTION

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Haverich, A et al, 1994, IDS # C9 of paper No:4, or Ried, CJ et al, 1988, IDS # C42 of paper No:4, as evidenced by McCaffrey, PG et al, 1993, IDS # C29 of paper No:4 and Martinez-Martinez, S et al, 1997, Mol Cell Biol, 17(11): 6437-6447.

Claim 1 is drawn to a method of treating hypertrophy in a subject, comprising the step of inhibiting the function of NF-AT3 in a cardiomyocyte, wherein inhibition of NF-AT3 function inhibits hypertrophic gene expression, thereby treating hypertrophy.

Claim 1 reads on a method of treating hypertrophy in a subject, comprising the step of inhibiting the function of NF-AT3 in a cardiomyocyte, using a compound that inhibits the function of NF-AT3.

Haverich, A et al teach treating of transplant coronary disease, comprising administering cyclosporin A.

Reid et al teach treating patients with cardiac transplantation cyclosporin A (p.399, first column, under immunosuppression).

Although Haverich, A et al and Reid et al do not teach cardiomyocytes, it is well known in the art that the heart comprises cardiomyocytes, which are inherently exposed to cyclosporin A.

McCaffrey, PG et al teach that cyclosporin A blocks the dephosphorylation of NFATp and the appearance of NFAT in nuclear extracts (p.750, second column, last paragraph bridging third column).

Martinez-Martinez, S et al teach that cyclosporin A inhibits NFATp by preventing the dephosphorylation and translocation into the nucleus of NFATp, which comprises NFAT1, NFATc and NFAT3 (p.6437).

Because the method of the prior art comprises the same method step as claimed in the instant invention using the same composition, i.e. a compound that inhibits the function of NF-AT3, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS
April 22, 2002

SUSAN UNGAR, PH.D
PRIMARY EXAMINER